

WHAT IS CLAIMED IS:

1. A method for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition, the method comprising determining a genotype of said
5 subject at a polymorphic site in the subject's toll-like receptor 2 (TLR-2) sequence, wherein said genotype is indicative of an ability of the subject to recover from the inflammatory condition.
2. The method of claim 1, wherein the polymorphic site is at position 201 of SEQ ID
10 NO:1 or at a polymorphic site in linkage disequilibrium thereto.
3. The method of any one of claims 1-2, further comprising comparing the genotype so determined with known genotypes which are known to be indicative of a prognosis for recovery from:
15 (i) the subject's type of inflammatory condition; or
(ii) another inflammatory condition.
4. The method any one of claims 1-3, further comprising determining the TLR-2
20 sequence information for the subject.
5. The method any one of claims 1-4, wherein said determining of genotype is performed on a nucleic acid sample from the subject.
6. The method of claim 5, further comprising obtaining a nucleic acid sample from
25 the patient.
7. The method any one of claims 1-6, wherein said determining of genotype comprises one or more of:
30 (a) restriction fragment length analysis;
(b) sequencing;
(c) hybridization;

- (d) oligonucleotide ligation assay;
 - (e) ligation rolling circle amplification;
 - (f) 5' nuclease assay;
 - (g) polymerase proofreading methods;
 - 5 (h) allele specific PCR; and
 - (i) reading sequence data.
8. The method of any one of claims 1-7, wherein the risk genotype of the subject is indicative of a decreased likelihood of recovery from an inflammatory condition or
- 10 an increased risk of having a poor outcome.
9. The method of claim 8, wherein the subject is critically ill and the risk genotype is indicative of a prognosis of severe cardiovascular or respiratory dysfunction.
- 15 10. The method of claim 8 or 9, wherein the risk genotype comprises at least one T nucleotide at position 201 of SEQ ID NO:1.
11. The method of any one of claims 1-7, wherein the protective genotype of the patient is indicative of an increased likelihood of recovery from an inflammatory
- 20 condition.
12. The method of claim 11, wherein the subject is critically ill and the protective genotype is indicative of a prognosis of less severe cardiovascular or respiratory dysfunction.
- 25 13. The method of claim 11 or 12, wherein the protective genotype is homozygous for the A nucleotide at position 201 of SEQ ID NO:1.
14. The method of any one of claims 1-13, wherein the inflammatory condition is selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress
- 30

Syndrome (ARDS), acute lung injury, aspiration pneumonitis, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for patients undergoing major surgery or dialysis, patients who are immunocompromised, patients on immunosuppressive agents, patients with HIV/AIDS, patients with suspected endocarditis, patients with fever, patients with fever of unknown origin, patients with cystic fibrosis, patients with diabetes mellitus, patients with chronic renal failure, patients with bronchiectasis, patients with chronic obstructive lung disease, chronic bronchitis, emphysema, or asthma, patients with febrile neutropenia, patients with meningitis, patients with septic arthritis, patients with urinary tract infection, patients with necrotizing fasciitis, patients with other suspected Group A streptococcus infection, patients who have had a splenectomy, patients with recurrent or suspected enterococcus infection, other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococcemia, post-pump syndrome, cardiac stun syndrome, myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, *E. coli* 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia, HELP syndrome, mycobacterial tuberculosis, *Pneumocystis carinii*, pneumonia, Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, Dengue hemorrhagic fever, pelvic inflammatory disease, Legionella, Lyme disease, Influenza A, Epstein-Barr virus, encephalitis, inflammatory diseases and autoimmunity including Rheumatoid arthritis, osteoarthritis, progressive systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis, transplants including heart, liver, lung kidney bone marrow, graft-versus-host disease, transplant rejection, sickle cell anemia, nephrotic syndrome, toxicity of

agents such as OKT3, cytokine therapy, and cirrhosis.

15. The method of any one of claims 1-14, wherein the inflammatory condition is SIRS.

5

16. A method of identifying a polymorphism in a TLR-2 sequence that correlates with prognosis of recovery from an inflammatory condition in a subject, the method comprising:

10

- (a) obtaining TLR-2 sequence information from a group of subjects with an inflammatory condition;
- (b) identifying at least one polymorphic nucleotide position in the TLR-2 sequence in the subjects;
- (c) determining a genotype at the polymorphic site for individual subjects in the group;
- 15 (d) determining recovery capabilities of individual subjects in the group from the inflammatory condition; and
- (e) correlating genotypes determined in step (c) with the recovery capabilities determined in step (d)

15

thereby identifying said TLR-2 polymorphisms that correlate with recovery.

20

17. The method of claim 16, wherein the inflammatory condition is selected from the group consisting of: sepsis, septicemia, pneumonia, septic shock, systemic inflammatory response syndrome (SIRS), Acute Respiratory Distress Syndrome (ARDS), acute lung injury, aspiration pneumonia, infection, pancreatitis, bacteremia, peritonitis, abdominal abscess, inflammation due to trauma, inflammation due to surgery, chronic inflammatory disease, ischemia, ischemia-reperfusion injury of an organ or tissue, tissue damage due to disease, tissue damage due to chemotherapy or radiotherapy, and reactions to ingested, inhaled, infused, injected, or delivered substances, glomerulonephritis, bowel infection, opportunistic infections, and for patients undergoing major surgery or dialysis, patients who are immunocompromised, patients on immunosuppressive agents,

25

30

patients with HIV/AIDS, patients with suspected endocarditis, patients with fever,
 patients with fever of unknown origin, patients with cystic fibrosis, patients with
 diabetes mellitus, patients with chronic renal failure, patients with bronchiectasis,
 patients with chronic obstructive lung disease, chronic bronchitis, emphysema, or
 5 asthma, patients with febrile neutropenia, patients with meningitis, patients with
 septic arthritis, patients with urinary tract infection, patients with necrotizing
 fasciitis, patients with other suspected Group A streptococcus infection, patients
 who have had a splenectomy, patients with recurrent or suspected enterococcus
 infection, other medical and surgical conditions associated with increased risk of
 10 infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis,
 fungal sepsis, meningococemia, post-pump syndrome, cardiac stun syndrome,
 myocardial infarction, stroke, congestive heart failure, hepatitis, epiglottitis, *E. coli*
 0157:H7, malaria, gas gangrene, toxic shock syndrome, pre-eclampsia, eclampsia,
 HELP Syndrome, mycobacterial tuberculosis, *Pneumocystis carinii*, pneumonia,
 15 Leishmaniasis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura,
 Dengue hemorrhagic fever, pelvic inflammatory disease, *Legionella*, Lyme disease,
 Influenza A, Epstein-Barr virus, encephalitis, inflammatory diseases and
 autoimmunity including Rheumatoid arthritis, osteoarthritis, progressive systemic
 sclerosis, systemic lupus erythematosus, inflammatory bowel disease, idiopathic
 20 pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis,
 Wegener's granulomatosis, transplants including heart, liver, lung kidney bone
 marrow, graft-versus-host disease, transplant rejection, sickle cell anemia,
 nephrotic syndrome, toxicity of agents such as OKT3, cytokine therapy, and
 cirrhosis.

- 25
18. A kit for determining a genotype at a defined nucleotide position within a
 polymorphic site in a TLR-2 sequence, wherein knowledge of the genotype
 provides a prognosis of the subject's ability to recover from an inflammatory
 condition, the kit comprising;
- 30 (a) a restriction enzyme capable of distinguishing alternate nucleotides at the
 polymorphic site; or

- (b) a labeled oligonucleotide that is sufficiently complementary to an alternate nucleotide sequence at the polymorphic site so as to be capable of specifically hybridizing to said alternate nucleotide sequence, whereby the genotype of the polymorphic site may be determined; and
- 5 (c) optionally, instructions for use in determining the genotype.
19. The kit of claim 18, wherein a polymorphism site corresponds to position 201 of SEQ ID NO:1.
- 10 20. The kit of claim 18 or 19 further comprising an oligonucleotide or a set of oligonucleotides suitable to amplify a region including the polymorphic site.
21. The kit of claim 20, further comprising a polymerizing agent.
- 15 22. A method for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition, the method comprising determining a genotype for one or more polymorphic sites in the TLR-2 sequence for each subject, wherein said genotype is indicative of the subject's ability to recover from the inflammatory
- 20 condition and sorting subjects based on their genotype.
23. The method of claim 22 further comprising, administering the candidate drug to the subjects or a subset of subjects and determining each subject's ability to recover from the inflammatory condition.
- 25 24. The method of claim 23, further comprising comparing subject response to the candidate drug based on genotype of the subject.
- 30 25. A method for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of a gram positive infection, the method comprising determining a genotype for one or more

polymorphic sites in the TLR-2 sequence for each subject, wherein said genotype is indicative of the subject's likelihood of developing a gram positive infection and sorting subjects based on their genotype.

- 5 26. The method of claim 25 further comprising, administering the candidate drug to the subjects or a subset of subjects and determining each subject's ability to recover from the gram positive infection.
- 10 27. The method of claim 26, further comprising comparing subject response to the candidate drug based on genotype of the subject.
- 15 28. A method of treating a gram positive infection in a subject in need thereof, the method comprising administering to the subject an antibiotic agent, wherein said subject has a TLR-2 risk genotype.
- 20 29. A method of treating a gram positive infection in a subject in need thereof, the method comprising:
 (a) selecting a subject having a risk genotype in their TLR-2 sequence; and
 (b) administering to said subject an antibiotic agent.
- 25 30. A method of selecting a subject for treatment of a gram positive infection with an antibiotic agent, comprising identifying a subject having a TLR-2 risk genotype, wherein the identification of a subject with the TLR-2 risk genotype is predictive of an increased likelihood of gram positive infection.
- 30 31. The method of claims 28-30, wherein the antibiotic agent is a gram positive specific antibiotic agent.
32. The method of claim 31, wherein the gram positive specific antibiotic agent is selected from the following: linezolid; cloxicillin; methecillin; nafcillin; oxacillin; vancomycin; tazobacam; imipenem; carbenem; meropenem; clindamycin;

rifampin; a cephalosporin; a macrolide; a quinolone; trimethoprim-sulfamethaxazol; rifampin; amoxicillin; a penicillin; gentamicin; ceftriaxone; ampicillin; cefotaxime; doxycycline; ciprofloxacin; erythromycin and metronidazole.

5

33. The use of an antibiotic agent in the manufacture of a medicament for the treatment of a gram positive infection, wherein the subjects treated have a TLR-2 risk genotype.

10

34. The use of an antibiotic agent in the manufacture of a medicament for the treatment of gram positive infection in a subset of subjects, wherein the subset of subjects have a TLR-2 risk genotype.

15

35. The method or use of any one of claims 28-34, wherein the TLR-2 risk genotype is at position 201 of SEQ ID NO:1.

36. The method or use of claim 35, wherein the TLR-2 risk genotype has at least one A nucleotide at position 201 of SEQ ID NO:1.

20

37. The method or use of claim 35, wherein the TLR-2 protective genotype is homozygous for the T nucleotide at position 201 of SEQ ID NO:1.

38. The use of claim 33 or 34, wherein the antibiotic agent is a gram positive specific antibiotic agent.

25

39. The use of claim 38, wherein the gram positive specific antibiotic agent is selected from the following: linezolid; cloxicillin; methecillin; nafcillin; oxacillin; vancomycin; tazobacam; imipenem; carbenem; meropenem; clindamycin; rifampin; a cephalosporin; a macrolide; quinupristin-dalfoprisin; trimethoprim-sulfamethaxazol; rifampin; amoxicillin; a penicillin; gentamicin; ceftriaxone; ampicillin; cefotaxime; doxycycline; ciprofloxacin; erythromycin and metronidazole.

30

40. A method for determining a risk of developing a gram positive infection in a subject, the method comprising determining a genotype of said subject at a polymorphic site in the subject's toll-like receptor 2 (TLR-2) sequence, wherein said genotype is indicative the subject's risk of gram positive infection.
41. The method of claim 40, wherein the polymorphic site is at position 201 of SEQ ID NO:1.
42. The method any one of claims 40-41, further comprising determining the TLR-2 sequence information for the subject.
43. The method any one of claims 40-42, wherein said determining of genotype is performed on a nucleic acid sample from the subject.
44. The method of claim 43, further comprising obtaining a nucleic acid sample from the patient.
45. The method any one of claims 40-44, wherein said determining of genotype comprises one or more of:
- (a) restriction fragment length analysis;
 - (b) sequencing;
 - (c) hybridization;
 - (d) oligonucleotide ligation assay;
 - (e) ligation rolling circle amplification;
 - (f) 5' nuclease assay;
 - (g) polymerase proofreading methods;
 - (h) allele specific PCR; and
 - (i) reading sequence data.
46. The method of any one of claims 40-45, wherein the genotype of the subject is indicative of a subject's risk of developing a gram positive infection.
47. The method of claim 46, wherein the risk genotype has at least one A nucleotide at

position 201 of SEQ ID NO:1.

48. The method of claim 46, wherein the protective genotype is homozygous for T at position 201 of SEQ ID NO:1.

5

49. An oligonucleotide of about 10 to about 400 nucleotides that hybridizes specifically to a sequence contained in a *human* target sequence consisting of SEQ ID NO:1, a complementary sequence of the target sequence or RNA equivalent of the target sequence and wherein the oligonucleotide is operable in determining a polymorphism genotype.

10

50. An oligonucleotide of about 10 to about 400 nucleotides that hybridizes specifically to a sequence contained in a *human* target sequence consisting of SEQ ID NO:1, a complementary sequence of the target sequence or RNA equivalent of the target sequence and wherein said hybridization is operable in determining a polymorphism genotype.

15

51. An oligonucleotide probe selected from the group consisting of:
- (a) a probe that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:1 having a A at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:1 having a T at position 201; and
 - (b) a probe that hybridizes under high stringency conditions to a nucleic acid molecule comprising SEQ ID NO:1 having a T at position 201 but not to a nucleic acid molecule comprising SEQ ID NO:1 having a A at position 201.

20

25

52. An array of nucleic acid molecules attached to a solid support, the array comprising an oligonucleotide that will hybridize to a nucleic acid molecule consisting of SEQ ID NO:1, wherein the nucleotide at position 201 is A, under conditions in which the oligonucleotide will not substantially hybridize to a nucleic acid molecule consisting of SEQ ID NO:1 wherein the nucleotide at position 201 is T.

30

53. An array of nucleic acid molecules attached to a solid support, the array comprising an oligonucleotide that will hybridize to a nucleic acid molecule consisting of SEQ ID NO:1, wherein the nucleotide at position 201 is T, under conditions in which the oligonucleotide will not substantially hybridize to a nucleic acid molecule consisting of SEQ ID NO:1 wherein the nucleotide at position 201 is A.
54. An oligonucleotide of any one of claims 49 to 53, further comprising one or more of the following: a detectable label; a quencher; a mobility modifier; a contiguous non-target sequence situated 5' or 3' to the target sequence.
55. A computer readable medium comprising a plurality of digitally encoded genotype correlations selected from the TLR-2 genotype correlations in TABLE 1B, wherein each correlation of the plurality has a value representing an ability to recover from an inflammatory condition; or risk of developing a gram positive infection.